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Research article

Localization of impalpable breast lesions and detection of sentinel lymph nodes through magnetic methods

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ABSTRACT

Purpose: The most commonly used technique for guiding the surgical removal of impalpable breast lesions is wire-guided localization (WGL). Potential complications of WGL include wire migration, wire transection, patient discomfort, and pneumothorax. Recently, another possibility for preoperative localization of breast lesions trough small steel seeds was developed. A magnetic handheld probe can be used both for localization of breast lesions and sentinel lymph nodes (SLNs) detection.

Methods: In this study, we used a new technology for localizing breast lesions in conjunction with sentinel nodes (SLNs) detection through SPIO nanoparticles; both detected using a magnetic probe. The technique uses small steel markers (Magseed®) with magnetic properties, which are placed in breasts under ultrasonographic or mammographic guidance. 41 localization seeds were placed in 38 patients. In 27 patients with malignant tumors, simultaneous use of magnetic method for SLNs detection was used.

Results: In all 38 patients, breast lesions were accurately localized using this method. No interference between Magseed signals and SPIO tracer signals were observed during magnetic probe measurements. All tumors were exscised with tumor-free surgical margins. The SLN biopsy was successful in all patients undergoing this procedure. The SLN median detection rate was 3 nodes.

Conclusions: The new magnetic methods are reliable alternatives for localizing breast lesions and SLN detection. They are well tolerated by patients and they can avoid the disadvantages of WGL. They have the potential to make tumor localization and SLN biopsy procedures possible in facilities without a nuclear medicine department or where radioisotope availability is limited.

1. Background

Widespread use of screening mammography has resulted in increased detection of impalpable breast lesions. The most commonly used technique for guiding the surgical removal of these occult breast lesions is wire-guided localization (WGL) [1,2]. Hook wires, with a self-retaining tip, are placed into the occult lesion under ultrasound, X-ray mammographic stereotaxy, or magnetic resonance guidance. Since the guide wire is introduced into the breast at the point estimated to be closest to the lesion, the surgical approach is usually along the axis of the wire. Imprecise surgical localization may result in an unnecessarily large excised specimen or failure to find the lesion. Wire placement is most often performed on the day of surgery, which can create problems for radiology and surgical scheduling and can lead to delays in the operating theater [1,2].

Recently, another possibility for preoperative localization of breast lesions was developed; it is called the Magseed. The seeds are made of medical grade, low nickel, stainless steel, and measure 5.0×1.0 mm [3,4]. The properties of the magnetic seed allow it to be easily detected using a handheld magnetic probe in the same way that superparamagnetic iron oxide (SPIO) tracer is detected in sentinel lymph nodes [5]. Solutions of carboxydextran coated SPIO nanoparticles are increasingly used for SLN detection with comparable results with the standard dual technique (radioisotope ^{99m}Tc in combination with blue dye). SPIO can be used by surgeon in operating theatre, it eliminates the need for nuclear medicine facilities and it has not been associated with allergic reactions (opposite to blue dye).

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2. Materials & methods

2.1. Study design

Forty-one magnetic localization seeds were placed in thirty-eight patients in this single-institutional, cohort study between April 2018 and April 2019 at our Department. Written informed consent was obtained from all patients. The inclusion criteria covered patients with core biopsy-proven impalpable breast carcinomas or premalignant lesions eligible for breast-conserving surgery and patients with impalpable lesions with uncertain malignant potential. Patients with a pacemaker or implanted device in the chest wall, an iron/nickel or Sienna allergy, and pregnancy or lactation were excluded. The study was approved by the Comenius University and University Hospital of Bratislava Ethics Committee.

2.2. Localization procedures

The first thirty-one localizations markers (Magseed®, Endomagnetics Ltd., Cambridge, UK) were inserted, under ultrasound (Voluson S10, 6.0–15.0 MHz multi-frequency linear probe, GE Healthcare Corporate, USA) or stereotactic (Mammomat Inspiration, Siemens Healthcare GmbH, Germany) guidance under local anesthesia, directly into the center of the target lesions just prior to surgery (Fig. 1). The last ten markers were inserted under the same conditions, but on the day before surgery. Ipsilateral two-view mammography (mediolateral and craniocaudal views) was performed immediately after each localization procedure to confirm the position of the marker. One patient had bilateral seed placement, and two patients two seeds placed in the same breast.

2.3. Surgical procedures

In patients with a preoperative large core needle biopsy that indicated infiltrating breast carcinoma and/or ductal carcinoma *in situ* (DCIS), with a high risk of invasion, lymphatic mapping and sentinel lymph nodes biopsy (SLNB) were the initial surgical procedures. After induction of general anesthesia, 2.0 ml of SPIO nanoparticles (Sienna®, Endomagnetics Ltd., Cambridge, UK), diluted to 5.0 ml with physiological saline solution, was injected into the subareolar interstitial tissue, which was followed by 5 min of breast massage to promote migration of the magnetic tracer. SLN detection was then performed, but no sooner than 20 min after injection. In the last seven patients, SPIO nanoparticles were injected in the same way, but on the day before surgery.

Before the axillary skin incision, magnetic count numbers from the skin were measured using a 2nd generation magnetic probe (Sentimag®, Endomagnetics, Ltd., Cambridge, UK). Magnetic counts were also measured intraoperatively, in situ, and ex vivo in the SLNs, and in the remaining axillary nodes. SLNs were excised until the counts were lower than 10% of the highest count or a maximum of five nodes per patient had been removed. All SLNs were examined during an intraoperative cryosection consultation. In patients with metastases into SLNs, an axillary level 1 + 2 lymphadenectomy was performed. In two patients with invasive carcinoma and micrometastases in only one SLN, no additional axillary dissection was undertaken.

Prior to making the initial breast incision, magnetic count numbers were measured using the same Sentimag probe to find the localization hotspot for the impalpable breast lesion. The skin incision and further breast tissue preparation were done under repeated Sentimag probe monitoring (Fig. 2). The lesions, together with healthy margins of breast tissue, were excised an effort to get tumor-free surgical margins. After resection of the tumor, the marker was confirmed to be present in the excised tissue using the Sentimag probe. Simple tools were used for specimen labeling (Fig. 3). Two-view specimen radiography (mediolateral and craniocaudal view) provided confirmation of complete tumor resection and Magseed presence in the specimen [6,7] (Figs. 3–5).

2.4. Pathology

All SLNs underwent an intraoperative frozen-section evaluation. SLNs with macrometastases were indicated as positive. All lymph nodes were than postoperatively evaluated for micrometastases in formalin-fixed embedded serial sections using hematoxylin/eosin staining and immunohistochemistry with cytokeratin AE1/AE3 stains. The surgical specimens were coated with ink and fixed in 10% neutral-buffered formalin for 24 h. The fixed specimens were examined through serial sectioning. The sections were then stained with hematoxylin and eosin. Immunohistochemistry was used for evaluation of estrogen, progesterone, and HER2 receptors, as well as the Ki67 proliferation index and assessment of myoepithelial cell integrity. Specimens with invasive cancer, with "no ink on tumor," and DCIS specimens with tumor-free margins < 2 mm were evaluated as specimens with negative surgical margins, according to current guidelines [8–10].

3. Results

A total amount of 41 seeds was placed in 38 patients. The mean age of our group of patients was 56.5 years and the mean BMI was 27.2. Tumor characteristics of all surgically treated impalpable breast lesions are shown in 1. The median diameter of the lesions, measured during breast imaging, was 12 mm (IQ range = 7.5 mm), while the median diameter measured during histopathology was 15 mm (IQ range = 7 mm). There were twenty-six cases of infiltrating breast carcinoma diagnosed. Additionally, a residual impalpable infiltrating carcinoma, after six cycles of neoadjuvant chemotherapy, was found in one patient. Three patients presented with DCIS, four patients had ADH, three patients had sclerosing adenosis, and in one patient a benign phyllodes tumor was found in the surgical specimens. Three patients

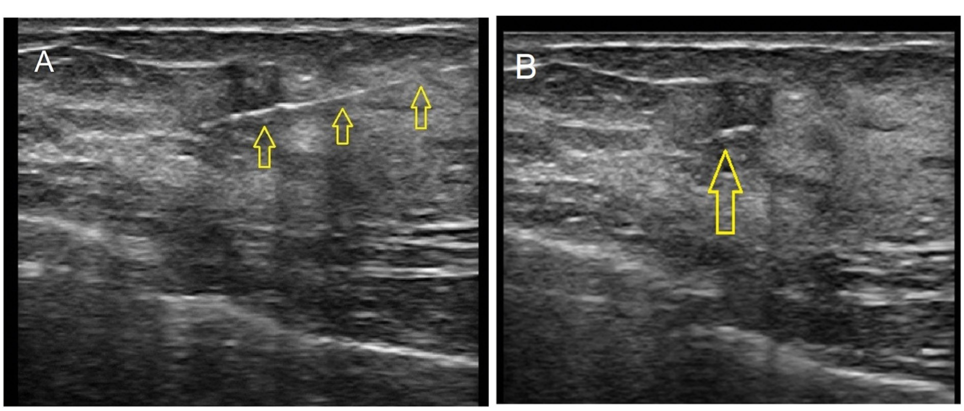

Fig. 1. Insertion of a Magseed through a needle deployment (arrows) under ultrasound guidance (A). The Magseed is seen in the middle of the lesion (B).

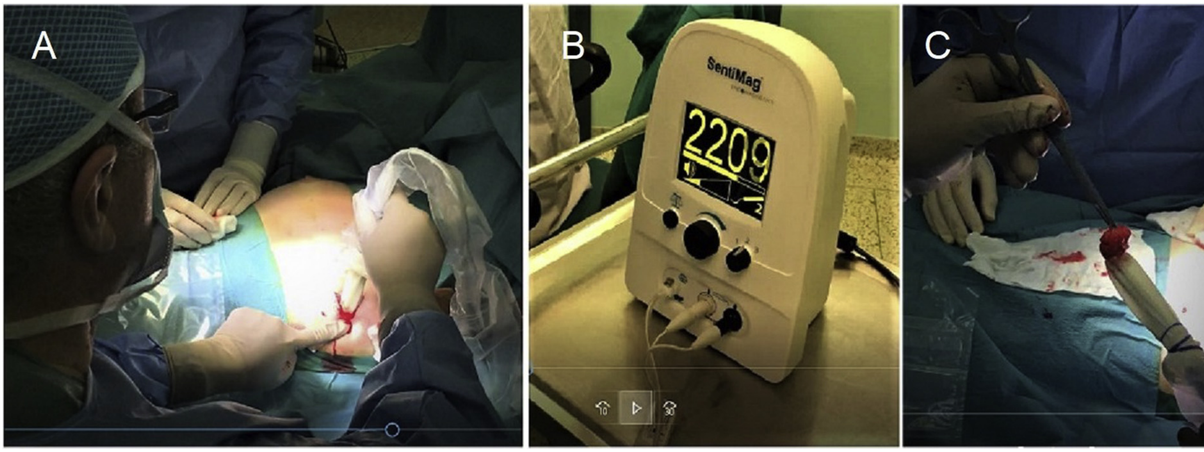

Fig. 2. Surgeon uses the Sentimag probe to localize the Magseed in the breast (A) and in the surgical specimen (C). The Sentimag base unit (B) displays a numerical count and produces an audio tone depending to the distance of the seed and/or sentinel nodes from the detector probe.'.

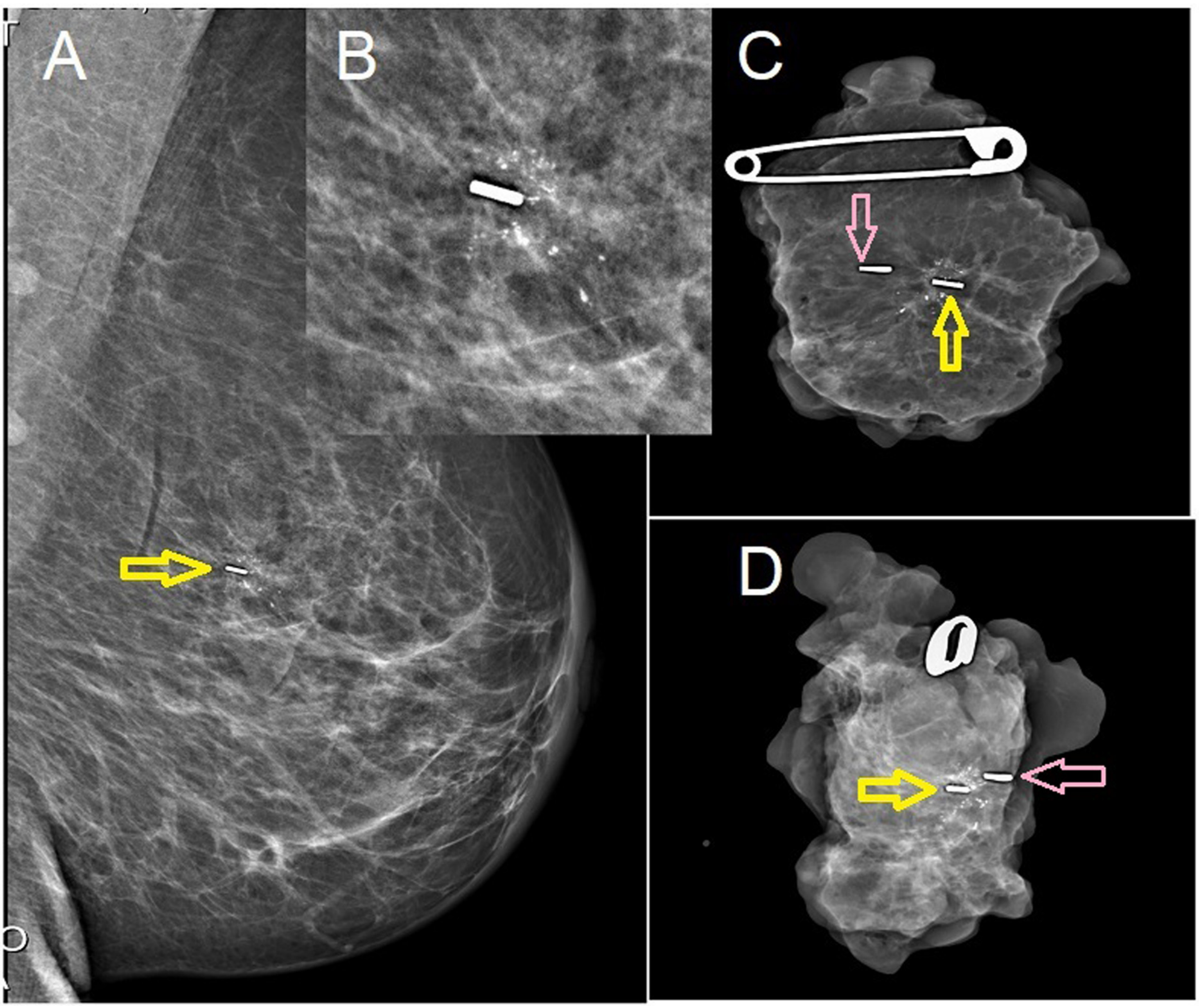

Fig. 3. An impalpable lesion in the left breast, localized with Magseed (yellow arrows) (A). A cluster of suspicious microcalcifications in detailed view (B). Specimen radiography in craniocaudal (C) and mediolateral (D) views. The closing pin (cranial) and the titanium clip (ventral; pink arrows) serve as guides for orientation of the specimen. Histology: intermediate-grade DCIS, pTis (11 mm) N0(sn), tumor-free margins.

presented benign collumnar cells changes. In one patient, after an uncertain diagnosis of lymphoproliferative disease based on core needle specimens, a non-Hodgkin follicular lymphoma was confirmed in the surgical specimen using cytogenetic diagnostics.

All impalpable lesions were precisely localized using the Magseed method and accurately detected in the breast using the Sentimag system. The seeds were also easily recognizable by the pathologist during gross examination of specimens. All tumors were removed with safe surgical margins during the primary operation, and no additional re-excision of margins was needed. The median nodal detection rate

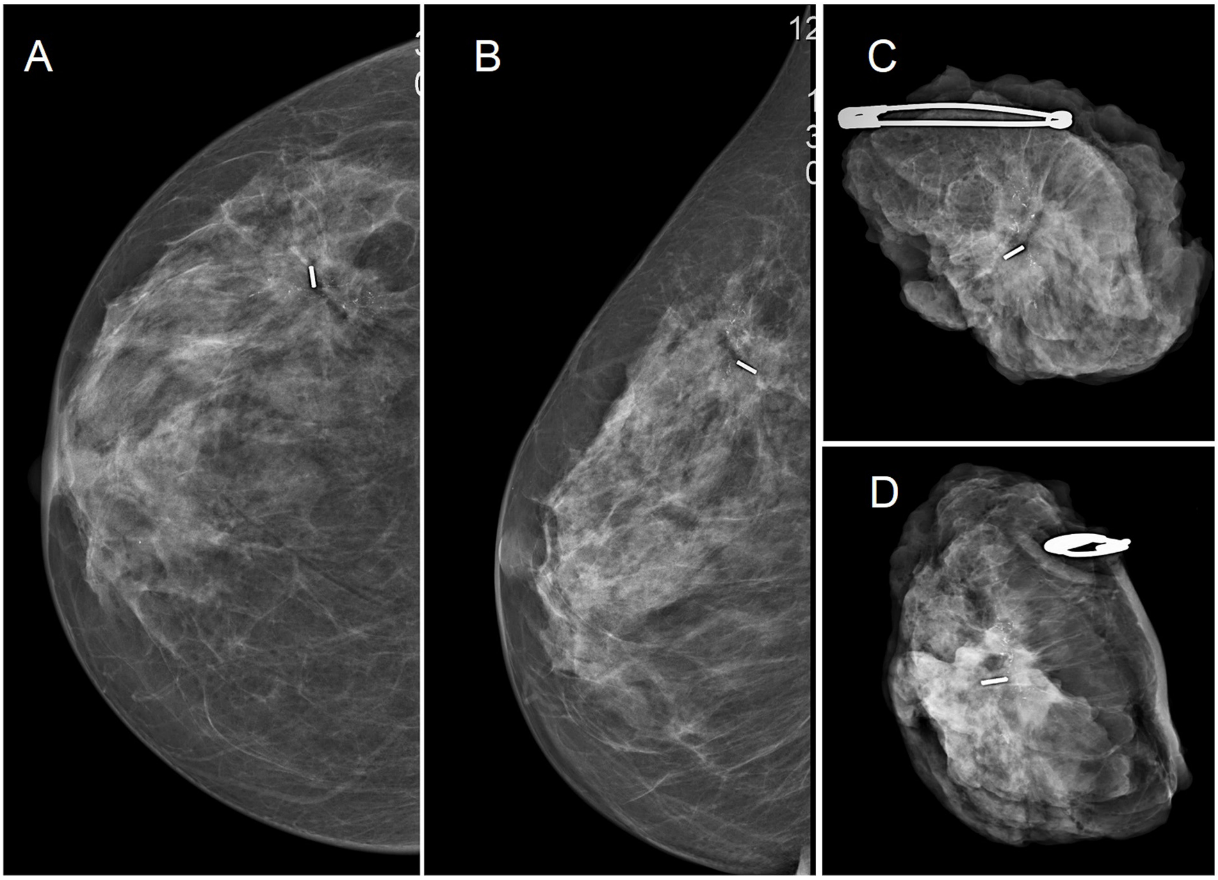

Fig. 4. Radial scar with microcalcifications in the right breast (A,B), localized with Magseed. Two-view specimen radiography (C,D) confirmed complete resection. Histology: IDC of micropapillary type, luminal A-like, pT2 (25 mm) N1b (3/10) M0, tumor-free margins.

(the proportion of SLNs detected per patient) was 3 nodes (IQ range = 2). Eight patients presented with metastases into the SLNs; additional axillary dissection was provided and in six of these patients further metastases were found in the non-sentinel axillary lymph nodes (Table 1).

No interference between Magseed signals and SPIO Sienna tracer signals were observed during magnetic probe measurements. The mean depth of Magseed insertion into the breast was 3.2 cm (range 1.5–7.3 cm). No complications or adverse events related to either seed placement or surgery were recorded. No migration of the Magseed in the breast from the time of its placement to the time of surgery was observed.

4. Discussion

For breast-conserving surgery on small, impalpable tumors, accurate tumor localization is essential [1]. For several years, the standard technique for intraoperative tumor localization of clinically occult tumors has been wire-guided localization (WGL), in which a hook wire is placed into the tumor under ultrasound, x-ray mammography, or MRI guidance. However, the WGL procedure is not without problems. WGL complications include wire migration before or during surgery, wire transection, patient discomfort, and pneumothorax [1,2]. This has led to the development of other guidance techniques, including radio-guided occult lesion localization (ROLL) and radio-guided seed localization (RSL). The ROLL technique uses a nonspecific radioisotope injected into the tumor under stereotactic or ultrasonographic guidance [11]. The exact localization of the primary tumor can be assessed intraoperatively using a handheld gamma-probe. RSL works in a similar fashion but uses an implantable ^{125}I encapsulated titanium seed as the radioactive guide. The seed can also be detected using a gamma-probe. After resection of the primary lesion, the probe can also be used to search for SLNs [12]. RSL, ROLL, and wire localization are equally reliable [11,12], however, RSL and ROLL suffer from high regulatory barriers and administrative burdens due to their use of radioactive materials.

The new magnetic method described in this study is an alternative way to localize breast lesions. In 2018, Price et al. [3] and Harvey et al. [4] published their first clinical experience with this method. Both studies concluded that Magseed is an effective and accurate means of preoperative breast lesion localization. In the study by Harvey et al. [4], 29 Magseed devices were placed into the breasts of 28 patients, 24 under ultrasound guidance and five under stereotactic guidance. One patient had bilateral seed placement. Twenty-seven of 29 Magseeds were placed directly into the target lesion, and all Magseeds were retrieved. There were no complications or adverse events related to either seed placement or surgery. However, the goal of the study was to assess feasibility and marker migration. This is why the seeds were used to localize the lesions in patients where mastectomy had been provided. In the study of Price et al. [3], 64 patients underwent the Magseed localization procedure. They reported that the method provided an effective means for preoperative breast lesion localization. The localization procedure with Magseed is well tolerated by patients and it can avoid the potential disadvantages of WGL. Magseed received FDA clearance for long-term (up to 30 days) soft tissue implantation in February 2018 and the CE mark of approval, by the EMA, in September 2017.

The use of SPIO nanoparticles in breast surgery has mainly been focused on their role in the identification of metastatic lymph node involvement. Lymphatic mapping and SLN detection using SPIO nanoparticles were found to be noninferior to the standard method

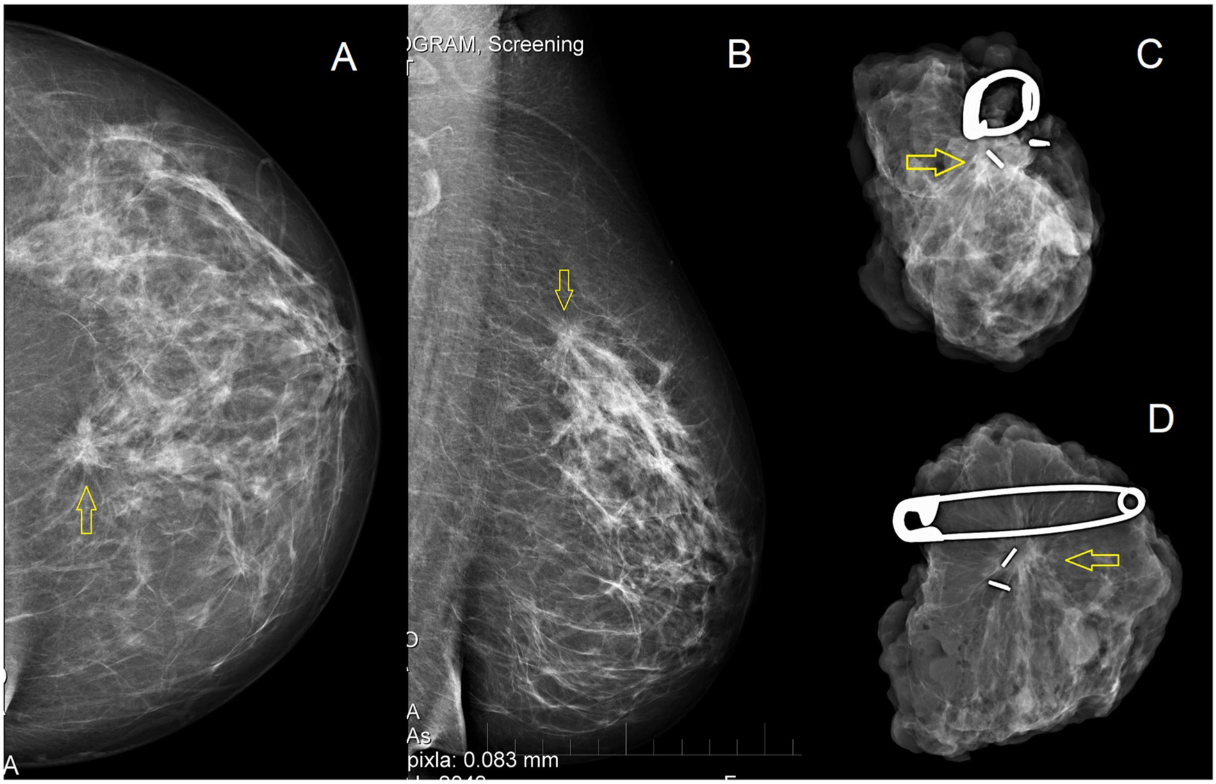

Fig. 5. Impalpable stellate lesion in the left breast in craniocaudal (A) and mediolateral (B) view marked with a Magseed. Specimen radiography in craniocaudal (C) and mediolateral (D) views for radical resection confirmation. Histology: infiltrating tubulo-lobular carcinoma, pT1c (14 mm) N1mi (sn) M0, grade 2, luminal A-like subtype, tumor-free margins.

(radioisotope ^{99m} Tc in combination with blue dye) in three meta-analyses of results from controlled clinical trials [13–15]. In addition, the magnetic technique had a high identification rate and a significantly higher lymph node retrieval rate [13]. Karakatsanis et al. [16] reported that the use of SPIO, as the sole tracer, was a safe alternative with results comparable to those of the standard dual technique. The SentiNot trial found that if SPIO was injected at the time of primary surgery for DCIS, SPIO outperformed isotope and blue dye in detection of sentinel nodes during further dissection in cases where an invasive component was found in the primary specimen (40 of 40 versus 26 of 40 women; $P < 0.001$) [17].

Our department surgically treats about 120 breast cancer patients per year. We have used the Sienna/Sentimag system for SLNs detection for the last 6 years. In 2018 we reported our initial experience with the simultaneous use of magnetic localization of impalpable breast tumors as well as magnetic SLNs detection [5]. In all ten patients with impalpable breast tumors we were able to accurately localize the tumors using the magnetic method and all tumors were resected with safe margins. The patients from the preliminary report are involved in our study. At the same time, Hersi et al. [18] reported on their experience with this combined method in a group of thirty-two patients recruited from two hospitals in Sweden. The Magseed localization procedure in combination of peritumoral injection of SPIO was performed by radiologists about three days before surgery (range 0–25). All 32 patients underwent a microscopic radical resection, and no seed migration was noticed. SLN detection using SPIO and a magnetic probe was successful in all patients and the median number of SLNs retrieved was two. The authors concluded that this novel technique seemed to overcome the limitations of wire- or radioiodine seed-guided surgery and provided radical excisions without the removal of excess breast tissue [18]. In our study, the surgeon performed the typically periareolar injection of SPIO in operating room after induction of general anesthesia. As described above, 2.0 ml of Sienna were diluted to 5.0 ml with saline solution. This volume of injection is perceived painfully by some patients, especially those with small breasts. We did not proceed *of label* use of Sienna without dilution.

Brown skin staining after a SPIO injection is one of the undesirable side effects of this method. Skin discoloration after SPIO tracer application was present in 35.5% of patients in the Nordic SentiMag trial [15]. It shaded away faded progressively in size and color over time to 21% of patients after a year. In our opinion, half of the patients had skin discoloration up to 6 months postoperatively, some of them even one year. Another drawback in using SPIO are artifacts in postoperative magnetic resonance breast imaging. Recently, Krischer et al. [19] refered impaired breast MRI after a mean follow-up time of 42 months in half of the 24 patients after Sienna injection. Further research is needed to investigate the diagnostic impact of these artifacts on patients follow-up. A new version of SPIO (SiennaXP®) is now tested in volumes of 1.5 and 1.0 ml without dilution [20]. This might further reduce skin staining, and it might reduce artefacts in postoperative MRI. Peri-tumoral injection can reduce staining with a similar SLN detection rate [21].

5. Conclusion

In our study, all thirty-eight patients with impalpable breast tumors had their tumors accurately localized using the magnetic method. We found no interferences between Magseed signals and SPIO Sienna tracer signals during magnetic probe measurements. All tumors were excised during the initial procedure, and no re-excision of surgical margins was needed. The SLNB procedure was successful in all 27 patients. The SLN median nodal detection rate was 3 nodes (IQ range = 2). This new technology has the potential to surmount the hurdles associated with the use of radioisotopes, i.e., availability and the need for a specialized department of nuclear medicine, as such the technology can be used to increase the success rate of SLNB procedures as well as improving

Table 1
Tumor characteristics of the impalpable breast lesions.

Patient ID	Ø lesion (breast imaging)	Ø lesion (histol.examin.)	tumor typing	tumor grading	ER/PR (%/%)	HER2 (+/-)	resection margins	SLN detected	SLN status	ALN status
1	20	20	phyllodes tumor	N/A	N/A	N/A	negative	–	–	–
2	4	6	ADH	N/A	N/A	N/A	negative	–	–	–
3	9	11	IDC	2	95/70	0	negative	2	0/2	–
4	8	12	IDC	2	100/100	1+	negative	3	0/3	–
5	12	16	IDC	2	99/30	0	negative	5	0/5	–
6	5	15	DCIS	2	95/95	0	negative	4	0/4	–
7	11	15	IDC	2	99/70	2+	negative	5	0/5	–
8	15	15	IDC	3	90/60	0	negative	3	2/3	4/11
9	15	25	IDC	2	90/0	0	negative	5	3/5	6/25
10	12	21	DCIS	3	5/5	3+	negative	4	0/4	–
11	18 + 7	17 + 8	IDC + fibroadenoma	2	99/90	0	negative	3	0/3	–
12	11	15	IDC	2	95/60	0	negative	5	0/5	–
13	20	25	IDC	2	95/2	0	negative	5	3/5	0/4
14	20	17	Sklerosing adenosis	N/A	N/A	N/A	negative	–	–	–
15	18	8	ADH	N/A	N/A	N/A	negative	–	–	–
16	25	30	IDC	3	0/0	0	negative	5	1mi/5	–
17	15	16	IDC	1	98/100	1+	negative	5	0/5	–
18	13	11	IDC	2	95/80	1+	negative	5	0/5	–
19	18	23	IDC	2	100/95	0	negative	2	2/2	1/7
20	5	6	Collumnar cell changes	N/A	N/A	N/A	negative	–	–	–
21	12	10	IDC	3	0/0	3+	negative	3	3/3	6/6
22	15 + 8	20 + 10	IDC + collumnar cell changes	2	90/40	3+	negative	2	0/2	–
23	15	17	Sklerosing adenosis	N/A	N/A	N/A	negative	–	–	–
24	12	12	Folicular lymphoma	N/A	N/A	N/A	negative	–	–	–
25	9	5	IDC	1	99/2	0	negative	4	0/4	–
26	11	8	Sklerosing adenosis	N/A	N/A	N/A	negative	–	–	–
27	10	10	ILC	2	60/10	2+	negative	3	0/3	–
28	14 + 25	14 + 21	IDC (multifocal)	3	90/10	3+	negative	2	2/2	4/14
29	9	11	IDC	1	100/100	0	negative	2	0/2	–
30	10	13	IDC	1	100/100	2+	negative	4	0/4	–
31	22	20 + 15 + 12	ILC (multifocal)	2	100/100	3+	negative	3	2/3	0/5
32	11	13	IDC	3	95/0	0	negative	3	0/3	–
33	13	14	ILC	2	100/90	2+	negative	3	1mi/3	–
34	12	11	DCIS	2	100/100	1+	negative	4	0/4	–
35	22	25	IDC (mucinous)	1	95/95	0	negative	2	0/2	–
36	8 + 5 + 3	6 + 5 + 3	ADH (multifocal)	–	–	–	negative	–	–	–
37	16	15	Collumnar cells changes	–	–	–	negative	–	–	–
38	9	10	ADH	–	–	–	negative	–	–	–

Ø lesion = largest diameter of the lesion in mm.
ADH = atypical ductal hyperplasia.
DCIS = ductal carcinoma in situ.
IDC = infiltrating ductal carcinoma.
ILC = infiltrating lobular carcinoma.
ER = estrogen receptors (% of positive).
PR = progesteron receptors (% of positive).
HER2 = human epidermal growth factor receptor 2 (negative = 0, 1+, equivocal = 2+, positive = 3+).
SLN detected = number of detected sentinel lymph nodes with Sentimag/Sienna.
SLN status = number of positive sentinel lymph nodes/number of examinated sentinel lymph nodes.
ALN status = number of positive axillary lymph nodes (non SLN)/number of examinated axillary lymph nodes (non SLN) in cases with axillary lymph nodes dissection.

tumor localization in facilities where using ROLL and RSL are not options.

Ethics approval and consent to participate

The study was approved by the Comenius University and University Hospital of Bratislava Ethics Committee. Written informed consent was obtained for patient participation and for the publication of all associated data and images.

Consent for publication

Written informed consent was obtained from patients for the publication of all associated data and images.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

K. Pohlodek performed patient examinations, breast imaging, localization breast procedures, breast surgery, and analyzed and interpreted patient data regarding the disease. K. Pohlodek was the primary author of the manuscript. P. Sečanský performed interventional breast procedures and breast surgery. I. Haluzová performed breast imaging examinations. I. Mečiarová performed histological examinations of core needle biopsies, surgical specimens, and analyzed and interpreted the patient data regarding the histology.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgment

Not applicable.

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